REMARKS

Claims 30-63 are pending in the instant application. Claims 30-63 have been rejected. Claims 30 and 38-40 have been objected to. Claims 30, 37, 38, 42 and 51 have been amended. No new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Objection to Claims 30 and 38-40

Claims 30 and 38-40 have been objected to for the following informalities. With respect to claim 30, the use of the word "the" before composition is incorrect as composition has not been previously specified. With respect to claims 38-40, the dependency of claim 38 is incorrect.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 30 to be drawn to "A composition" and corrected claim 38 to depend from claim 37.

Withdrawal of these objections is respectfully requested.

II. Rejection of Claims 44-46 under 35 U.S.C. 112, second paragraph

Claims 44-46 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention The Examiner suggests that there is insufficient antecedent basis for the limitation of "nucleic acid".

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 42, from which claims 44-46 ultimately depend, and claim 51 to state "nucleic acid". Support for this amendment is provided in the specification at page 7, lines 5-6.

Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims 30-34 under 35 U.S.C. 102(b)

Claims 30-34 have been rejected under 35 U.S.C. 102(b) as being anticipated by Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226). The Examiner suggests that Malovrh et al. discloses a composition comprising a sponge toxin, sponge toxin comprising poly-APS, sponge toxin obtained from *Renieri sarai*, wherein the sponge toxin has a molecular weight

between 5.0 kDa to 20 kDa.

Applicants respectfully traverse this rejection.

At the outset, it is respectfully pointed out that claim 30 has been amended in accordance with teachings in the specification at, for example, page 2, line 30 through page 3, line 13, to recite a composition comprising a reversible pore-forming sponge toxin.

MPEP 2131 and the case law are clear; a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference.

Nowhere does Malovrh teach that the polymeric alkylpyridinium salts isolated from the marine sponge *Reniera sarai* are reversible pore-forming sponge toxins. Instead, Malovrh teaches divalent cations to be required to close pores (see paragraph 2 at page 225 of Malovrh).

Nor would it be inherent in teachings of Malovrh that their polymeric alkylpyridinium salts would have this capability.

MPEP 2112 and the case law are clear; to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the

thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

The polymeric alkylpyridinium salts of Malovrh behave in a different manner to the instant claimed sponge toxins. Specifically, the formation of reversible pores was attenuated by Zn2+ in the present invention, i.e. prevented from forming when Zn2+ was added prior to or concurrent with poly-APS, however Zn2+ added after poly-APS had no effect on already formed pores (see line 33 page 31 to line 32 page 32 of the instant specification). This is the opposite of that taught in Malovrh. Accordingly, extrinsic evidence indicates that the polymeric alkylpyridinium salts of Malovrh are not the same as the instant invention.

Since Malovrh neither expressly nor inherently describes a composition comprising a reversible pore-forming sponge toxin, this reference cannot anticipate the instant claimed invention.

Withdrawal of this rejection is therefore respectfully requested.

IV. Rejection of Claims 30-40 and 60-63 under 35 U.S.C. 103(a)

Claims 30-40 and 60-63 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226).

Applicants respectfully traverse this rejection.

As discussed in Section III, supra, claim 30 has been amended in accordance with teachings in the specification at, for example, page 2, line 30 through page 3, line 13, to recite a composition comprising a reversible pore-forming sponge toxin.

As also discussed in Section III, Malovrh et al. does not teach a composition comprising reversible pore-forming sponge toxin. Nor does Malovrh et al. suggest such a sponge toxin.

Instead, while the poly-APS of Malovrh et al. is disclosed to "produce discrete lesions in erythrocyte membranes" (column 2, page 224), the author's consider that divalent cations are required to close the resulted pores (para 2, page 225). Indeed, in the experiments disclosed in Malovrh, "Zn2+ was inhibitory even when added after

poly-APS" (column 1, page 224). In contrast, the reversible pores formed by the reversible pore-forming sponge toxin of the present invention close of their own accord, i.e. they are a transient event in the lipid bilayer after which the integrity of the bilayer recovers. Furthermore, repeated poration can be obtained in the present invention without the occurrence of cytotoxic damage, leaving functioning cells intact. Even sensitive voltage-gated Ca2+ channels were functional after a period of poration (lines 21 to 28 on page 29). There is no evidence of cell survival following lysis in Malovrh.

Furthermore, the formation of reversible pores was attenuated by Zn2+ in the present invention, i.e. prevented from forming when Zn2+ was added prior to or concurrent with poly-APS, however Zn2+ added after poly-APS had no effect on already formed pores (line 33 page 31 to line 32 page 32). This is the opposite of that taught in Malovrh.

Clearly a person skilled in the art would not, and could not, arrive at the claimed composition or method for the reversible formation of membrane pores from the teachings of Malovrh. Thus, this reference cannot render obvious the instant claimed invention. See MPEP 2143, and

in particular Section G, which states that the rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve **the claimed invention** (emphasis added) and that there would have been reasonable expectation of success".

Withdrawal of this rejection under 35 U.S.C. 103(a) is respectfully requested.

V. Rejection of Claims 41-49 under 35 U.S.C. 103(a)

Claims 41-49 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Woude et al. (PNAS 1997 Vol. 94, p. 1160-1165) in view of Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226). The Examiner suggests that it would have been obvious to one of ordinary skill in the art to substitute the pyridinium compound in the transfection method as taught by Woude et al. with the pyridinium compound (poly -APS) as taught by Malovrh et al. to achieve a method for transfection of a macromolecule into a cell in vitro, because the substitution of one known element for another would have yielded a predictable result to one of ordinary skill in the art.

Applicants respectfully traverse this rejection.

With regard to Woude et al. suggested by the Examiner to disclose transfection of DNA, a macromolecule, into cells by means of pyridinium compounds, it is respectfully pointed out that such transfection is by an entirely different mechanism to that of the present invention. Woude et al. discloses vesicle-mediated transfection into cells which is entirely different to the reversible pore-forming mechanism of action of the claimed sponge toxins.

Accordingly, the suggested modification by the Examiner, to substitute the pore-forming molecule of Malovrh et al. into the method of Woude et al., would change the principle of operation of the method of Woude et al. MPEP 2143.01, subsection VI, is clear; if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.

Further, while Malovrh et al. discloses poly-APS which is capable of forming pores, the poly-APS disclosed therein is not suitable for transfection because the membrane

permeabilization which Malovrh et al. induce is not reversible and thus results in cell death. This is evidenced by the cytotoxic nature of the poly-APS disclosed in Malovrh et al.

Accordingly, contrary to the Examiner's suggestion, a person skilled in the art would not combine the teachings of Woude et al. and Malovrh et al. because Woude repeatedly emphasizes the importance of ensuring reduced toxicity of the compounds used for transfection while Malovrh repeatedly emphasizes the cytotoxic nature of the poly-APS used therein. A person skilled in the art would therefore not consider the poly-APS of Malovrh to be suitable for use in the transfection methods of Woude et al. and would not combine the teachings of these two references.

Further, even if the teachings of these two references were combined as suggested by the Examiner, they would not result in a method for transfection of macromolecules as claimed in the present invention. Firstly, pore formation is unlikely to occur and secondly, if it did occur it would likely result in cell death. This is because the method of Woude et al. requires premixing of DNA and pyridinium compounds ("Transfection assay" page 1161) whereas pore

formation by the poly-APS of the present invention is attenuated when the poly-APS is mixed with DNA prior to pore formation (lines 12 to 16, page 47). Thus, membrane permeabilization would be unlikely to occur using the poly-APS of Malovrh in the protocols of Woude. Further, even if the poly-APS of Malovrh did generate pores, cell death would likely be the result because there is no evidence that the pores are reversible.

Claims 41 to 49 are thus clearly not obvious over Woude et al. in view of Malovrh et al.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

VI. Rejection of Claims 50-59 under 35 U.S.C. 103(a)

Claims 50-59 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Woude et al. (PNAS 1997 Vol. 94, p. 1160-1165) and Arendt et al. (Neuroscience, 1998, Vol. 85, No. 4, p. 1337-1340) in view of Ballard C.G. (European Neurology, 2002, VO. 47, P. 64-70) and further in view of Bunc et al. (Toxicon 2002 Vol. 40, P. 843-849). The Examiner suggests that it would have been obvious to one of ordinary skill in the art to substitute the transfection agent in the transfection method of Woude et al. with a

composition comprising a sponge toxin (pyridinium compound) as taught by Bunc et al. to provide a method for transfection of a macromolecule in vivo, because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. The Examiner suggests that since, at the time the invention was made it was well known in the art that among therapeutic approaches in the treatment of Alzheimer's disease (AD) the use of cholinesterase inhibitors has been most successful, a person of ordinary skill would have been motivated to modify the method of Arendt et al. by applying a sponge toxin, a potent acetylcholinesterase inhibitor, as taught by Bunc et al. to provide a method of studying a neurological disease.

Applicants respectfully traverse this rejection.

With respect to claims 50-53, as already discussed in Section V, supra, the method taught by Woude et al. of transfection of DNA, a macromolecule, into cells by means of pyridinium compounds is by an entirely different mechanism to that of the present invention. Woude et al. discloses vesicle-mediated transfection into cells which is

entirely different to the pore-forming mechanism of action of the claimed sponge toxins.

Accordingly, the suggested modification by the Examiner, to substitute the poly-APS of Bunc et al. (which relates to the same poly-APS of Malovrh et al. (see col. 2, page 844 of Bunc et al.)) into the method of Woude et al. would change the principle of operation of the method of Woude et al. MPEP 2143.01, subsection VI is clear, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.

Further, while Malovrh et al. discloses the poly-APS (also used by Bunc et al.) is capable of forming pores, the poly-APS disclosed therein is not suitable for transfection because the membrane permeabilization which Malovrh et al. induce is not reversible and results in cell death. This is evidenced by the cytotoxic nature of the poly-APS disclosed in Malovrh et al. Toxicity of the poly-APS in vivo was confirmed by Bunc et al.

Accordingly, contrary to the Examiner's suggestion, a

person skilled in the art would not combine the teachings of Woude et al. and Bunc et al. because Woude repeatedly emphasizes the importance of ensuring reduced toxicity of the compounds used for transfection while Bunc et al. emphasizes the lethal nature of the poly-APS used therein. A person skilled in the art would therefore not consider the poly-APS of Bunc et al. to be suitable for use in the transfection methods of Woude et al. and would not combine the teachings of these references.

Woude et al. also provides no evidence and makes no suggestion that the methods disclosed therein could be repeated in vivo. Accordingly, this reference fails to provide any reasonable expectation of success with respect to the invention of claims 50-53. Secondary references of Arendt et al. and Ballard fail to remedy deficiencies as these references are unrelated to in vivo transfection methods or sponge toxins. The secondary reference of Bunc et al. actually teaches away from any reasonable expectation of success as the poly-APS molecule described therein is lethal.

Accordingly, claims 50 to 53 are clearly not obvious over the cited combination of references.

As to claims 54 to 59, Woude does not hint or suggest at a model or method for studying neurological disease, never mind such a model or method utilizing sponge toxins as claimed in the present application.

Bunc et al. discusses the possible lethal effects of poly-APS and concludes that the principle mechanisms of poly-APS lethality are haematological and vascular effects. At no point does Bunc et al. mention neurological disease or use of sponge toxins in a model or method for studying neurological disease. Bunc et al. also provides no mention of tau protein or phosphatase inhibitor and thus provides absolutely no means or motivation for a person skilled in the art to arrive at the present invention.

Arendt et al. discloses use of okadaic acid to induce hyperphosphorylation of tau and thus generate a model/method for studying Alzheimer's disease. However, there is no disclosure of the use of sponge toxins or indeed of applying exogenous tau protein to the hippocampus of a rodent. The application of okadaic acid in Arendt et al. serves only to hyperphosphorylate endogenous sources of tau. This disclosure is thus very far removed from the present invention and provides absolutely no means or

motivation for a person skilled in the art to arrive at the present invention.

Finally, Ballard discusses the importance of cholinesterase inhibitors in the treatment of Alzheimer's disease. However, there is no disclosure of sponge toxin, tau protein or phosphatase inhibitor. As such, Applicants fail to see the relevance of this document to the patentability of the instant claimed invention.

MPEP 2143.01, Section III and the case law are clear; the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. KSR International Co. v. Teleflex Inc., 550 U.S. ___, ____, 82 USPQ2d 1385, 1396 (2007). Clearly the resultant combination of two references (Woude et al. and Bunc et al.) silent with respect to a model or treatment for neurological disease with two references silent with respect to the compositions of the present invention (Ballard and Arendt et al.) in no way provides to one of ordinary skill in the art a predictable result for a rodent model for use in the study of neurological disease or treatments thereof comprising a rodent having undergone

application of a composition comprising a sponge toxin to the hippocampus or a method of studying a neurological disease by applying a composition comprising a sponge toxin to a rodent as claimed.

In view of the above comments, it is submitted that a person skilled in the art would not combine the teachings of Woude et al., Arendt et al., Ballard and Bunc et al. to arrive at the invention of claims 50 t0 53 or claims 54 to 59. In this respect, as the documents are in different technical fields (for example Woude relates to vesicle mediated transfection and Ballard relates to treatments for Alzheimer's disease with no overlap between the two) it is submitted that a person skilled in the art would not necessarily be aware of all the documents and would certainly not have any motivation to combine them. Furthermore, as none of the documents disclose the use of sponge toxins as claimed in the present invention, a combination of all the documents would still not result in the present invention. The present invention is thus non-obvious over all the cited prior art.

Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

VII. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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